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Circuit Models for Robust, Adaptive Neural Control

Roger Mailler
UNIVERSITY OF TULSA, THE

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Final Report

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14. ABSTRACT
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During this project, we made significant gains in understanding how the neurons and body walls muscles of C. elegans work together to form a robust neural circuit. Using a multi-pronged approach, we explored the function of individual cells using electrophysiological methods, developed new techniques for measuring neural circuit behavior using optogenetics, and built the most accurate model of worm locomotion to date. Together, these components helped us determine that the C. elegans neural circuit for locomotion achieves robustness using four circuit motifs. Each of the patterns contains multiple redundancies combined with a set of overlapping feedback loops.

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Abstract

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Technical Report

1 Introduction

Taking the perspective that the best way to understand something is to construct it; this interdisciplinary project aims to reproduce the locomotion neural circuitry used by *C. elegans* to drive a virtual model in our highly detailed 3D *C. elegans* simulator [4]. The goal of this project, therefore, is to develop an understanding of the basic motifs used by nature in developing complex, adaptive control systems. This goal can be further refined into three specific project objectives:

1. Develop a biologically accurate computational model of the locomotion circuitry used by *C. elegans*.
2. Validate the model by demonstrating that it produces the various locomotion modalities in a physics-based simulation environment.
3. Verify that the model accurately reproduces the robustness and adaptability seen in the living organism using comparative video analysis.

We believe that the locomotion circuit used by *C. elegans* forms the basis for a number of more complex circuits that are found in higher order organisms. In other words, by understanding this simple circuit, we hope to provide a foundation for understanding much more complex behaviors.

During this project, we made steady progress in accomplishing our project goals. This progress comes in the form of new discoveries about the function of the muscle cells, the development of new techniques for measuring muscle activity, a new neural modeling technique, models of several neural types found in *C. elegans*, and advances in our neural and physics modeling software. As a reminder, this project has five primary goals:

1. Perform direct measurements of the cells that form the C. elegans locomotion circuitry.
2. Create computational models of the individual cells and the circuit they form.
3. Develop a physics-based simulation environment to validate the models.
4. Develop software to quantify C. elegans locomotion in various environments
5. Validate the computational model within the simulation and verify the results against real data

The rest of this report will cover each of these goals in turn.

2 Background

Caenorhabditis elegans is a small (~1.2 millimeter) nematode found in rotting fruit in many parts of the world. It feeds on bacteria and is neither parasitic nor pathogenic. Although capable of sexual reproduction, most laboratory strains reproduce primarily as self-fertilizing hermaphrodites, with each adult hermaphrodite producing approximately 300 progeny. *C. elegans* (see Figure 1) is a very simple organism, with only 959 somatic cells in the adult hermaphrodite [1]. Although the total number of cells is small, they are differentiated into the standard array of tissues: 302 neurons, 95 body muscle cells, 32

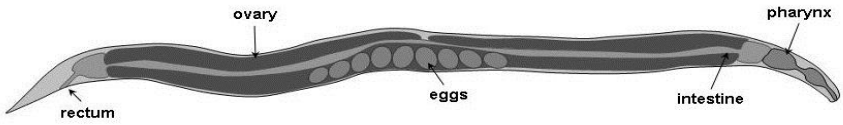

Figure 2: Basic anatomy of an adult hermaphrodite

gut cells, etc. In addition, the position, morphology, and lineage of each cell are reproducible from animal to animal [2] [3]. Because of the small size of the animal, the relatively small number of neurons, and the reproducible nature of the nervous system, it has been possible to provide an almost-complete synaptic connectivity map of the adult hermaphrodite nervous system [4] [5] [6].

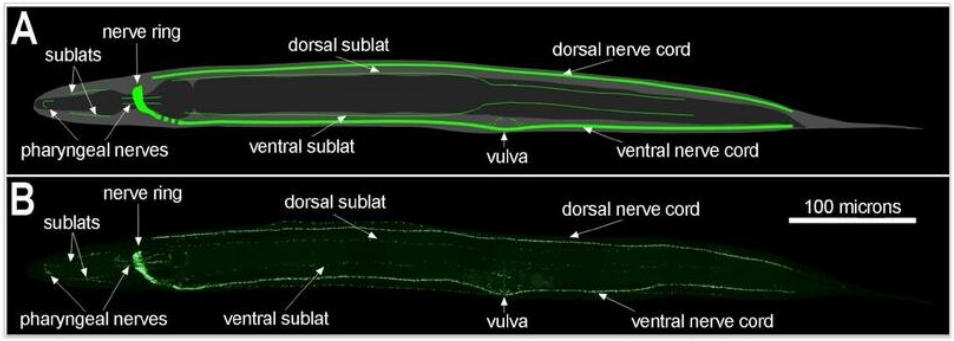

Figure 1: C. elegans nervous system [12]

C. elegans move using muscle cells that are arranged in four rows, two dorsal and two ventral. Each row consists of 23 or 24 muscle cells that are arranged in an interleaving pattern [7]. Toward the anterior of the worm, the cells occur in overlapping pairs with less overlap and pairing occurring toward the posterior. This particular arrangement of cells restricts the movement of the worm to dorsal and ventral bending. As a result, the animal lies on its side and propagates sinusoidal ventral-dorsal waves as it crawls on a flat agar surface (longitudinal ridges on lateral surfaces of the cuticle, called alae, act like "treads" to provide traction on moist surfaces).

The *C. elegans* nervous system has several distinctive features (see Figure 2). Most important among these are the nerve ring, dorsal nerve cord, and ventral nerve cord. This work focuses primarily on the dorsal and ventral nerve cords. Contained within these regions are a set of 69 **motor neurons** that innervate the body wall muscles posterior of the nerve ring. These neurons, traditionally grouped into **7 Classes** (11 AS cells, 9 DA, 7 DB, 6 DD, 12 VA, 11 VB, and 13 VD) based on morphological criteria [8], are responsible for forward and reverse wave propagation. The A-type (VA and DA) neurons are active during reverse locomotion, while the B-type (VB and DB) are active during forward locomotion. D-type motor neurons act as a cross inhibitory mechanism to prevent muscles on both the dorsal and ventral

sides from contacting simultaneously. Finally, AS neurons act to control dorsal muscles during reverse locomotion.

This very rudimentary understanding of the function of these neurons along with an incomplete mapping of the interconnections between them have led to a simplified view of how this circuit functions (see Figure 3). However, researchers have largely been unable to explain how the types of locomotion seen in the worm could be achieved using a circuit that consists of simple cross inhibition between the dorsal and ventral sides.

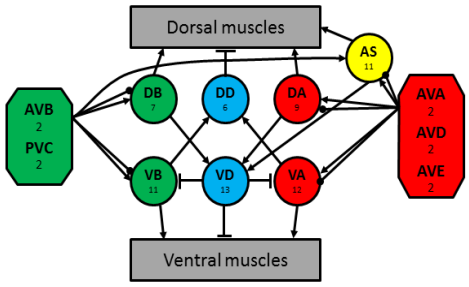

Figure 3: Basic motor circuitry diagram (adapted from [11])

3 Accomplishments

3.1 Goals 1 & 4: Measure the worm and quantify the locomotion

Doing direct measurements of the activity of the cells within C. elegans is difficult because of the small size of the organism and its internal pressure. Performing these measurements is a tedious and time consuming task that requires patience and a steady hand. Despite the inherent difficulties, the Wang lab has developed techniques for obtaining measurements using both patch clamp and voltage clamp methods from several of the neurons. During this project they made several important discoveries.

The first discovery was to relate the activity of the A-type motor neurons and the activity of the muscle cells. Figure 4 and Figure 5, for example, shows that there is a strong correlation between the activity of VA5 and one of the muscle cells it innervates.

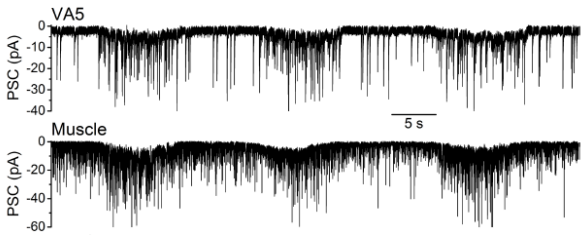

Figure 4: Currents of VA5 and the muscle cell it innervates

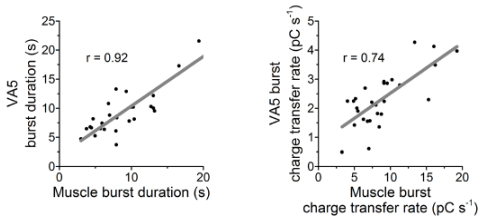

Figure 5: Correlation of motor neuron and muscle cell activity

Furthermore, they were able to show that these bursts led directly to a change of Ca^{2+} in the muscle cell, which indicates muscle contraction.

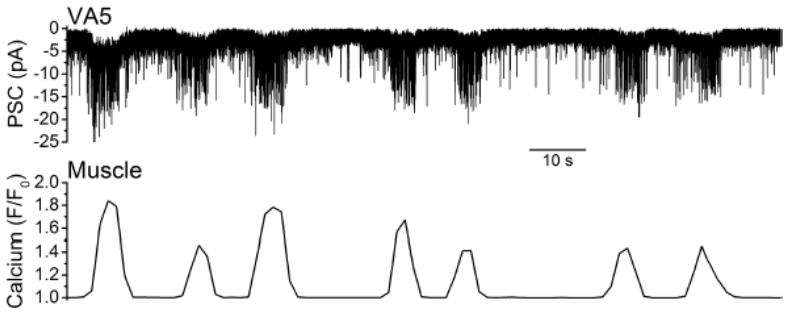

Figure 6: VA5 activity leads to muscle Calcium level changes

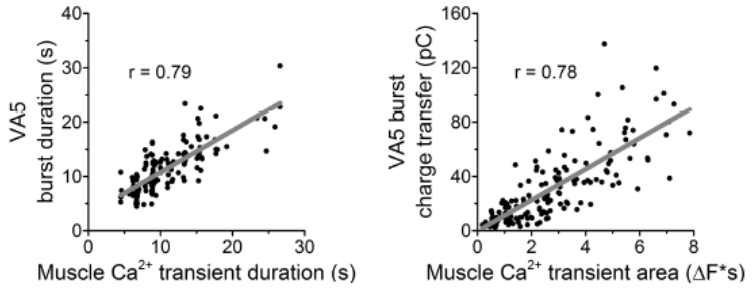

Figure 7: Significant correlation between motor neuron and muscle cell activity

During this project, the Wang lab also obtained whole cell currents from 3 classes of motor neurons: A, B, and D type. Using a voltage clamp, they found that the A and B type neurons are very similar in behavior, in that they both appear to be biphasic. This would indicate that these cells lack voltage gated K^+ channels that are largely responsible for the falling phase of action potentials. They also found that D-type neurons have graded membrane potentials. D-type are the primary inhibitory neuron used to control muscle cells. Figure 8 shows the results of these measurements.

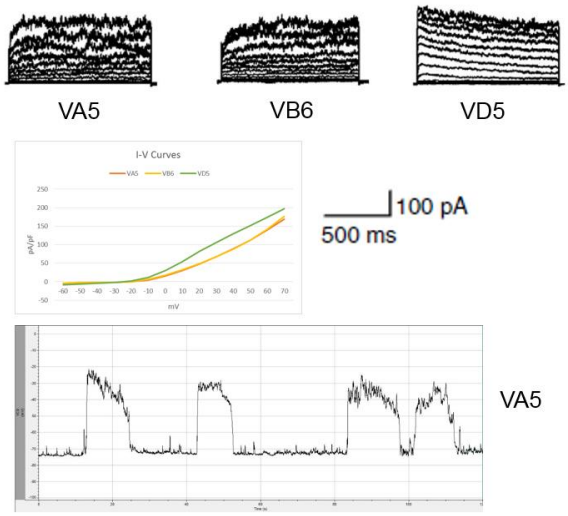

Figure 8: Whole cell currents of A, B, and D type motor neurons

During this project, the CNAS lab developed new methods for measuring the activity of the muscle cells using optical techniques. With the acquisition of our new microscope through the DURIP program, we have been able to develop a new toolchain (see Figure 9) for tracking worms while simultaneously recording their muscle activity.

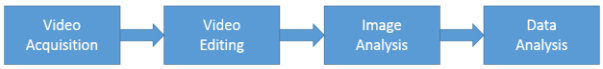

Figure 9: New data acquisition toolchain

The toolchain consists of 3 new software packages, a new Arduino-based sequencer, and includes a new video compression format. The first step in the process is the acquisition of video data. To perform this step, we developed a specialized software package to control our Leica DMI 8. The software package works by interfacing with the automated components on the microscope to control the stage position, focus, objectives, filter cubes, etc. It also interfaces with the Andor Zyla 6.3 sCMOS camera to acquire images at up to 100 frames per second. Finally, using a custom designed sequencer, the software can set up lighting sequences that are hardware triggered by the camera in a closed loop pattern. This software package consists of over 22,000 lines of mixed C++/Java code that is used to control this new piece of equipment.

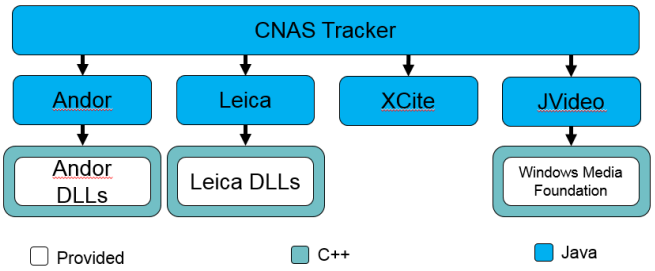

Figure 10: CNAS Tracker software package

Figure 10 shows the layout of this new software package. Using Dynamic Link Libraries from Andor, Leica, and Microsoft (manufacturers of the camera, microscope and Windows), we developed a set of Java Native Interface wrappers. These wrappers enabled us to control the camera and microscope and to read and write video files using Java. We then developed control software for these devices and finally created the CNAS Tracker.

A typical acquisition experiment begins by placing a single worm on a tracking petri dish. The dish is then loaded onto the microscope. The operator then uses the CNAS Tracker to create a tracking sequence, which details the lighting conditions that will be used. Usually, this consists of rapid light switching between white transmitted light and blue reflected light. The worm is then acquired using the software and software-based tracking begins. Finally, the operator starts recording the video, which also triggers the sequence.

From a software perspective, when a new experiment begins, the software downloads the sequence into the sequencer and tells the camera to operate in hardware triggered mode. The sequencer then waits for a ready signal from the camera, which tells it to change the lighting to the next configuration in the sequence, and sends a trigger signal to the camera. This process occurs completely independently from the computer.

Within the computer a process is setup to grab 2048 X 2048 images from the camera as quickly as possible. The white light images are then analyzed to determine the position of the worm and the stage is moved to keep the worm in the center of the video frame. The images are compressed and stored for later analysis. This entire process occurs in under 10 ms allowing for capture rates of up to 100 frames per second.

To make the process work so quickly with so much data, we developed a new video compression format based on the LZ4 compression algorithm. This new format, which we called Rapid Video Compression (RVC), stores information about the experimental conditions along with the video itself. However, because the compression has to occur so quickly we only achieve a 30% size reduction on a typical video. This means that videos can be very large. To give an idea of how large, a typical 10 minute video can easily be larger than 100 GB (100 fps X 4 MB per frame X 600 seconds X 0.7). In addition, because we have our own format, we needed to develop additional tools to edit and analyze the video.

The next tool in the toolchain is the RVC editor (see Figure 11).This tool allows researchers to view, edit, and convert RVC files. The RVC Editor works in a similar manner to a typical video editing software package with a couple of distinct differences. The first difference is that users can control which

channels they want to view and save. This is important because these videos consist of alternating images based on the sequence. For example, the video may consist of every odd image being a brightfield and every even image being a fluorescence. Playing this video back in the editor would produce strange flashing images. The editor is also designed to cut video into pieces and save those

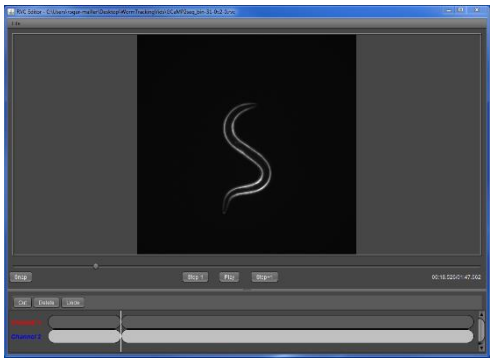

Figure 11: Screenshot of the RVC Editor

sections as independent files. This allows the researcher to remove bad sections of video for image processing.

Once the video is ready to be analyzed, it is loaded into the next component in the toolchain, the Muscle Analyzer (see Figure 12). This software package reads in RVC video and is capable of measuring the posture of the worm along with the intensity of the muscle cells from worms that contain calcium indicators in their muscle cells. In essence, this software allows us to directly measure the activity of the muscles while the worm is freely moving.

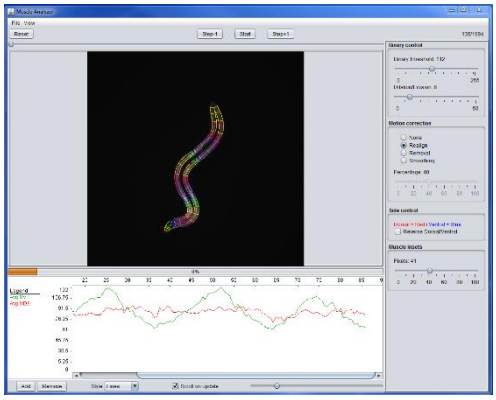

Figure 12: Analysis software for muscle activity

The analysis software works by using the alternating brightfield/fluorescence images taken by the CNAS tracker to first develop a template of the worm from the brightfield image and then use that template to measure the muscle cells in the subsequent fluorescence image. This is no easy feat as the shape and size of the worm can change significantly from frame to frame.

In the first step of the process, the brightfield image is converted to a binary image using a binary threshold. The body of the worm is converted to black and the background to white. A dilation, followed by erosion, operation is then used to fill in any small holes and to remove noise. A border following algorithm is used to determine the outline of the worm. This outline is cut into two halves (dorsal and ventral) by identifying the head and the tail based on their curvature. Using the two halves,

the centerline for the worm can be calculated. The result of this process is a descriptive model of the shape of the worm's body along with an outer border.

In the next step, the template is realigned with the worm's image in the fluorescence frame. The worm is then partitioned to locate the boundaries of the individual muscles and the average intensity of the signals within these boundaries are calculated. The results of the measurements are then saved to a text file for further processing.

Determining the muscle boundaries is more complex than it may first appear because, as mentioned previously, there is significant overlap between the cells. To accomplish this we first needed to determine the precise locations of the cells. This was done by using an image of a worm expressing GFP in its muscle cells (unc27::GFP) from WormAtlas [9] and hand tracing and measuring the cell locations (see Figure 13).

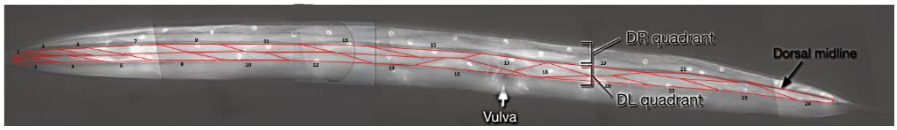

Figure 13: Muscle cell locations

This information was then fed into the muscle analyzer to determine the boundaries. However, with the overlap, it was necessary to alter the way we calculate averages. To do this we used a weighted average based on the distance from the cell's center. This has the effect of crediting the muscle that is closest to the pixel with the greatest contribution.

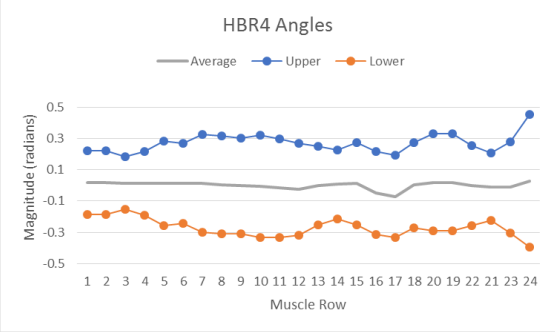

Figure 14: Bend angles of the body of C. elegans

The results of these experiments yielded some interesting findings. First, as can be seen in Figure 14, the bend angles of a wave during forward locomotion largely do not decrease as it moves down the body. This is in contrast to our previous findings [10]. Additionally, Figure 15 shows the average muscle activations during forward movement. As can be seen, on both the dorsal and ventral side of the worm there is significant activity of the muscles just behind the head of the worm. We believe that this area acts as the primary generator of force during movement.

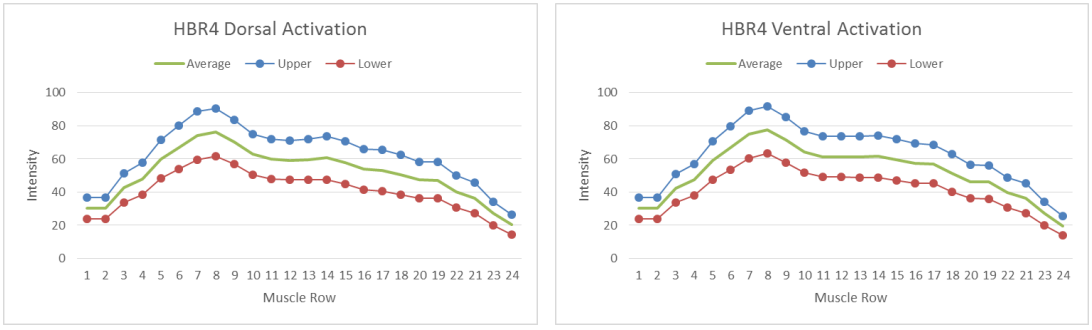

Figure 15: Muscle activity during forward locomotion

The next major finding can be seen in Figure 16. These graphs show the muscle activation patterns for two muscles on the dorsal and ventral sides of the same worm. As can be seen in these graphs, there are actually two different patterns of activation occurring. In first pattern, the dorsal muscle follows a sinusoidal pattern while the ventral muscle remain largely unchanged. In the second pattern, the dorsal and ventral muscles alternate in a pattern 180 degrees out of phase. This shows that although the dorsal and ventral sides are connected to one another, that their independency is more complicated than simple cross inhibition.

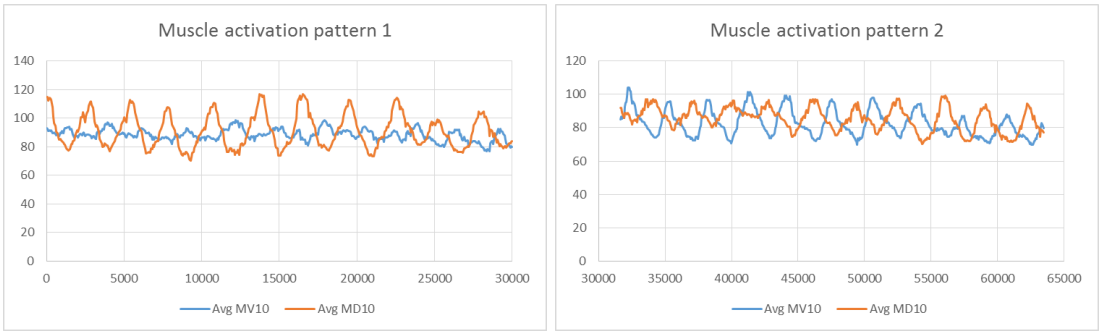

Figure 16: Patterns of muscle activation

3.2 Goal 2: Develop models

Using data we have obtained from the Wang lab, the CNAS lab has focused on developing two types of models. The first is a highly accurate model of the muscle cells using a Hodgkin and Huxley like formulation. During this period we augmented our existing model by figuring out the relationship between Ca^{2+} and the inactivation of the EGL-19 channel. We have also determined the relationship between Ca^{2+} levels and the activation of the SLO-2 BK type Ca^{2+} mediated K^{+} channel. These discoveries show that muscle cells certainly fire action potentials and that our model can faithfully reproduce the behavior of these cells giving different input currents. Figure 17 shows the results of simulating the behavior of muscle cells under various conditions.

The second accomplishment was the creation of a new method for simulating cells. Several techniques have been developed to simulate the activity of neurons. One of the most successful models comes

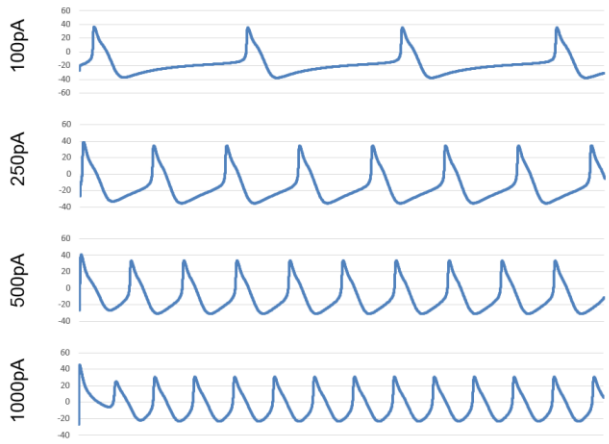

Figure 17: Activity of simulated muscle cell based on H&H model

from the work of Hodgkin and Huxley who created a conductance-based model using four Ordinary Differential Equations (ODEs). Their model is successful because it can predict the behavior of a neuron by modelling the changes in conductance of the ion channels in the cell. However, the H&H model is computational expensive because a significant number of samples must be done of the individual functions involved in the model as part of the computational integration.

Another technique that has gain popularity, particularly for large scale simulation, is the Integrate and Fire (IF) model. With the IF model, a single ODE is used to track the activation level of the neuron. When it reaches its threshold value, an action potential is generated in the form of a spike. IF models are often classified as current-based models, because they ignore the underlying mechanics involved in action potential generation and firing. Therefore, they are at least one step removed from biological reality in that they do not model the duration and intensity of the spike.

Because the muscle cells in C. elegans have lengthy action potentials (on the order of 100s of milliseconds) and many neurons do not fire a spike in response to input, we developed an intermediary model called the SBIF model. This current-based model still uses a single ODE, but is able to closely approximate the behavior of numerous cell types. The key insight used in this model is to recognize that neurons and muscle cells can only be in one of several states at a given instant. For example, a muscle cell can be at rest, firing, or recovering. Each of these phases has a different target voltage and change rate.

Using whole cell current data provided by the Wang lab, we developed SBIF models of the A, B, D-type and muscle cells of C. elegans. Figure 18 shows the behavior of a SBIF modeled muscle cell. Figure 19 shows the SBIF model being used to simulate the VA5 neuron.

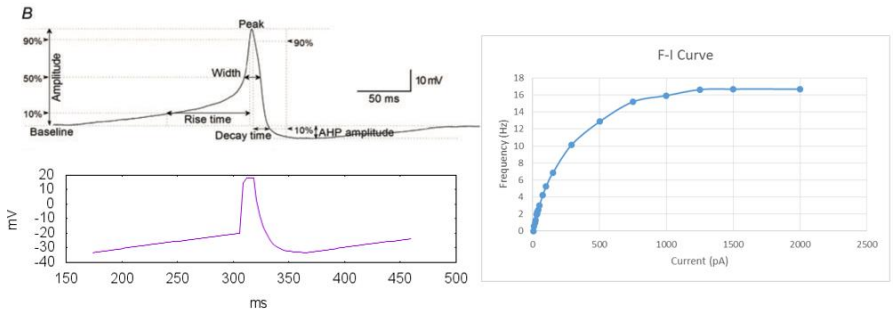

Figure 18: SBIF model of a muscle cell

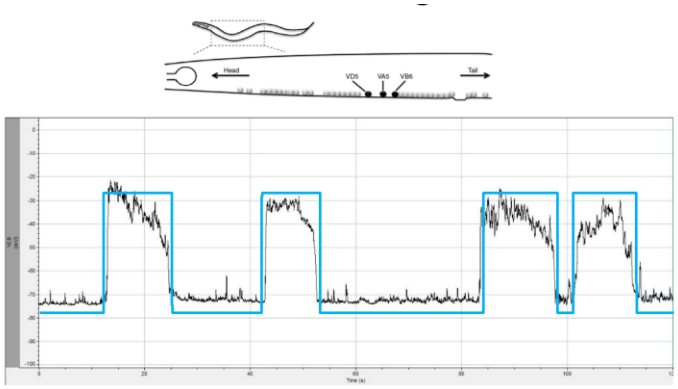

Figure 19: The simulation of VA5 using the SBIF model

As a continuation of our modeling activities, we began to analyze the neurons in the nervous systems to determine if there were any discernable patterns. We began by looking at the connection patterns of the primary neurons that are connected to the dorsal and ventral muscles. As Figure 20 and Figure 21

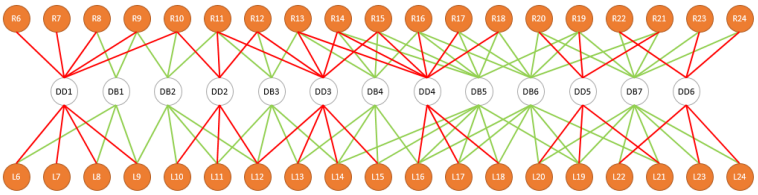

Figure 21: Muscle cell connection pattern on the dorsal side.

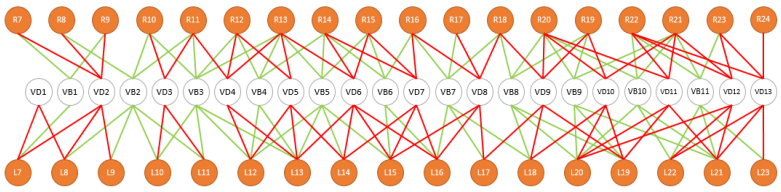

Figure 20: Muscle cell connection pattern on the ventral side.

show, the primary excitatory neurons (B-type) are staggered with the inhibitory neurons (D-type). This

is a pattern that has not been addressed by the community at large and makes a great deal of sense because it could mean that as the wave travels down the worms body, that the wave front suppresses the muscle cells behind it as well as the muscles on the opposing side. When we diagrammed the connections between the motor neurons (see Figure 22), we found that this hypothesis was partially supported. As you can see in this figure, when you look at the dorsal side motor neurons there definitely appears to be a pattern of anterior and cross inhibition until the 12th muscle group where the pattern changes. At this point, the ventral side still has anterior and cross inhibition, but the dorsal does not. It appears at this point that the dorsal side becomes a slave to the ventral side. This pattern occurs until muscle group 20 where multiple feedback loops occur on the ventral side and largely all of the activity on the dorsal side is mediated by DD6, which receives both excitatory and inhibitory signals from the ventral side.

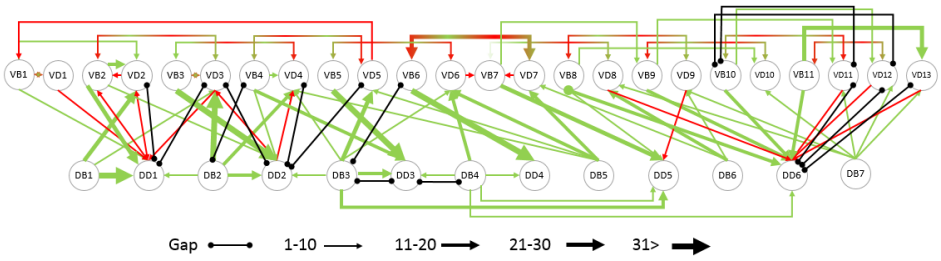

Figure 22: Motor neuron connectivity in C. elegans

These finds lead us to believe that there are four distinct regions within the locomotion circuitry used by the worm for movement. The first region is the head, which receives significant input from cells located in the nerve ring. The head controls direction. The second region occurs directly posterior of the nerve ring. Its connectivity and activation patterns suggest that it is responsible for providing forward force and slow turning behavior. Slow turning is mediated by inputs from a set of neurons called sublaterals. This region works by propagating the wave through the gap junctions between muscle cells, which are myogenic, while suppressing the opposing side and the muscle cells behind the wave as it moves forward. The third region is probably the simplest region as the ventral side takes control of the dorsal side to move the wave forward. Finally, the tail section works by feedback loops in ventral side, which work on DD6 alone to control the dorsal side. The ventral side also provides primary power for reverse locomotion.

3.3 Goal 3: Develop a physics based environment

Another major accomplishment during this project was a rebuild of the physics and neural simulator used in the lab. The original physics simulator was based on an open source game engine called the Java Monkey Engine (JME). JME is a very powerful game engine that uses OpenGL for graphics and the Open Dynamics Engine (ODE) to simulate physics. However, JME recently changed to version 3 and in the transition decided to use the Bullet physics engine instead of ODE. Bullet is a commercial grade game physics engine that uses numerous physics approximations to improve its runtime performance. These approximations, however, do not match reality.

As a result, we were forced to remove JME from our simulator and develop our own engine. Obviously there are a number of advantages to making this change including increasing performance by removing unnecessary components and having complete control over the code base.

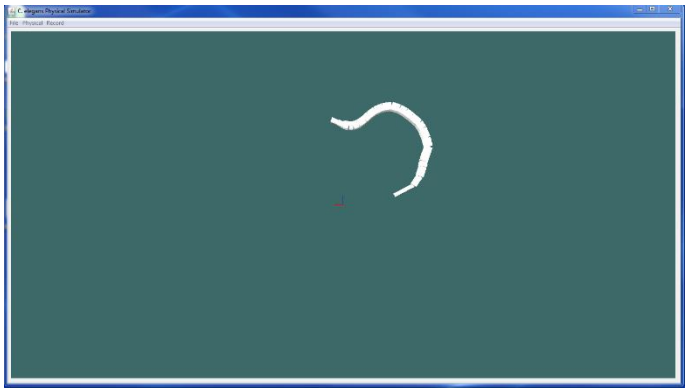

Figure 23: Worm physics simulator

Figure 23 shows our new simulation frame work, which is built directly on top of ODE and OpenGL. The engine includes a neural simulator as well as a new utility that allows us to use muscle activation data and feed it through to the simulator worm. This capability forced us to make a number of changes to the underlying physical model. The first is based on the muscle cell locations, we reduced the number of joints in the model from 24 down to 22. The placement of the joints was also modified to match the physiological measures that were described in Section 3.1. In addition, the new physics model accounts for the overlap between muscle cells.

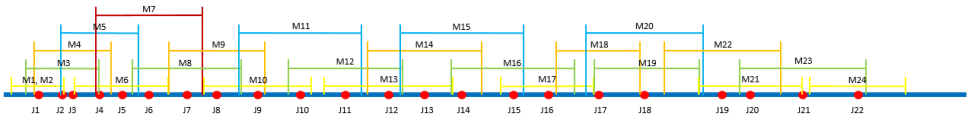

Figure 24: Model of muscle cell and joint interdependencies

Figure 24 shows the model of interdependencies between the muscle cells and the corresponding joints. In the model it is assumed that the muscle cells spread their force evenly over the joints they influence. This means, for example, that the force generated by M11 is spread to J9, J10, and J11 equally.

3.4 Goal 5: Verify the Model

The final goal of the project was to verify the models. Many of the models that have been presented in this report have been verified against real world data that was presented in their appropriate section. One model that remains to be validated is the physics model itself. To test the physics model, we collected data from living worms using our worm tracking software described in Section 3.1. As mentioned in Section 3.3 we then developed a nervous system playback capability in our physics simulation and integrated the new joint placements and muscle dependencies.

Figure 25 shows the results of the experiments. As you can see, even without detailed tuning, the simulation is a very close approximation to the behavior of the actual worm. The bend angle achieved as the worm moves are nearly a perfect match. However, the bend speeds of the simulated model are much slower than the actual worm. We believe this is cause by the improper scaling of muscle activation in the posterior of the worm when compared to the more powerful front. Additional tuning could certainly rectify this discrepancy.

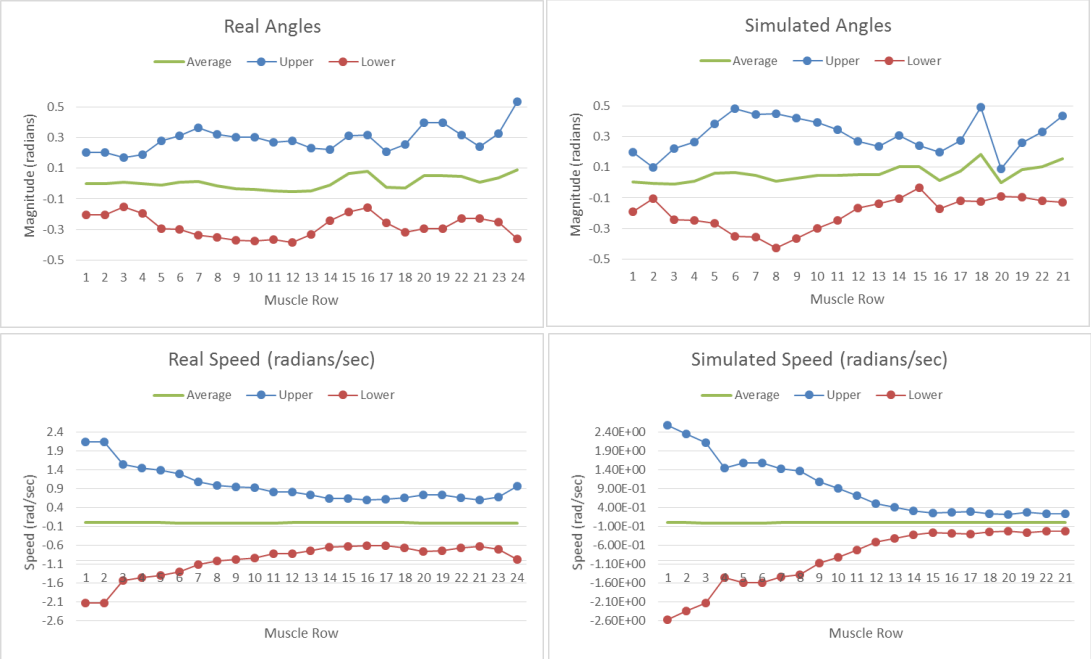

Figure 25: Results of comparing real to simulated worm

4 Conclusions

During the three years of this project, tremendous stride have been made to meet the projects goals. There have been myriad scientific discoveries and new techniques and technologies have been developed to accelerate future progress. Specifically, we have discovered that to understand how a nervous system functions, you cannot take a one size fits all approach to modeling the neurons involved. Additionally, simple models lead to simple results. Although there are some standard patterns to the way a nervous system functions, there are just as many inconsistencies as there are rules. For us, what has become most apparent is that we still have a great deal to learn from this seemingly simple creature.

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Abstract

This project seeks to reproduce the neural circuits used by the nematode Caenorhabditis elegans for locomotion. Utilizing only 113 neurons, this simple circuit drives the 95 body wall muscles to generate surprisingly complex and adaptive locomotion behavior. Recent advances in C. elegans electrophysiological techniques, which have resulted in a surge of new data, have made it possible to build an accurate computational model of C. elegans locomotion. This project combines the efforts of two labs with respective strengths in computational neuroscience/artificial intelligence and C. elegans electrophysiology to create this model. The Computational Neuroscience and Adaptive Systems (CNAS) lab at the University of Tulsa will generate a computational model based on anatomical and electrophysiological data of C. elegans, while the Wang lab at the University of Connecticut Health Center will perform electrophysiological experiments to validate the model and furnish any missing electrophysiological data for building the model.

During this project, we made significant gains in understanding how the neurons and body walls muscles of C. elegans work together to form a robust neural circuit. Using a multi-pronged approach, we explored the function of individual cells using electrophysiological methods, developed new techniques for

measuring neural circuit behavior using optogenetics, and built the most accurate model of worm locomotion to date. Together, these components helped us determine that the C. elegans neural circuit for locomotion achieves robustness using four circuit motifs. Each of the patterns contains multiple redundancies combined with a set of overlapping feedback loops.

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